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Evaluation and Clinical Value of Neuroendocrine Differentiation in Human Prostatic Tumors

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BACKGROUND. Prostate cancer, like other solid tumors, is a rather heterogeneous entity. More than 50% of all malignant prostatic tumors contain neuroendocrine-like cells, which cannot be attributed to small cell prostatic carcinoma or carcinoid-like tumors, which represent only 1–2% of all prostatic malignancies. Several investigators have reported that histopathologic determination of neuroendocrine differentiation in prostate carcinomas may have prognostic implications, while others have not confirmed these results. However, on the basis of experimental data, neuroendocrine-like cells appear to be involved in the emergence of androgen-independent cells and could be a target for new prostate cancer therapeutic strategies.

METHODS. The literature on the neuroendocrine phenotype of prostatic carcinoma is reviewed. This review summarizes most of the accumulated experimental and clinical data on the neuroendocrine phenotype in prostate cancer. We analyze the putative functions of neuroendocrine-like cells in prostate cancer progression and discuss the place of neuroendocrine phenotype biomarkers as diagnostic and prognostic factors in prostate cancer.

RESULTS. The fact that focal, patchy and heterogeneous clusters of neuroendocrine-like cells are frequently identified in organ-confined prostatic carcinoma probably accounts for the various evaluations of the predictive value of neuroendocrine histological patterns for the clinical outcome at this stage of the disease. The amount of neuroendocrine cells required to produce a detectable elevation in plasma chromogranin A has not yet been determined, but it is correlated with the number of chromogranin A-positive neuroendocrine (NE) cells. Despite the obvious current limitations of the application of neuropeptides as a serological test, this overview will try to more accurately define the possible roles of specific neuropeptides as prostatic cancer markers in diagnostic and monitoring protocols. The plasma chromogranin A level, in comparison with neuron-specific enolase (NSE), chromogranin B (CBG), pancreastatin, or secretogranin levels, appears to be the most useful neuroendocrine marker for determination of neuroendocrine differentiation of advanced prostatic adenocarcinoma.

CONCLUSIONS. Future studies on neuroendocrine should confirm whether neuroendocrine biomarkers, especially the chromogranin family of peptides, can be used as prognostic markers during the course of prostate cancer or for the selection of patients suitable for evaluation of new antineoplastic drugs known to be active against specific and aggressive subpopulations of tumor cells. *Prostate Supplement 8:43–51, 1998.*

KEY WORDS: **prostate cancer; tumor marker; neuroendocrine; chromogranin; neurosecretory system**

INTRODUCTION

Neuroendocrine differentiation has been demonstrated in a variety of carcinomas arising in various tissues. Prostatic carcinoma, non-small-cell lung can-

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cer, breast cancer, gastric carcinoma, and colorectal carcinoma are some of the tumors in which neuroendocrine differentiation has been described and suggested as a marker of poor prognosis [1,2]. The concept of neuroendocrine differentiation in prostatic carcinoma has become more widely recognized over recent years [3]. However, the clinical significance of this phenomenon remains unclear.

Neuroendocrine cells were first described in the prostate by Pretl [4], in 1944, and constitute part of a general endocrine regulatory system defined by Pearse [5], in 1966, who coined the term APUD to refer to the chemical characteristic of amine precursor uptake and decarboxylation common to the cells of this system. Peripheral components of this system include C cells of the thyroid, gastrointestinal, and pulmonary neuroendocrine cells and the pancreatic islets of Langerhans.

The presence of neuroendocrine cells has been demonstrated by silver-staining techniques, electron microscopy, or immunohistochemistry in the normal prostate, in benign prostatic hyperplasia (BPH), and in primary or metastatic prostatic adenocarcinoma (PC) before and after hormone therapy [6]. The presence of bioamines (serotonin) and peptides [7] (bombesin [8], vasoactive intestinal peptide, calcitonin [9,10], and somatostatin [11]) has also been reported in prostatic fluid. Peptide receptors and autocrine secretion of various bioamines and peptides (serotonin, somatostatin, bombesin, and calcitonin) have been reported in prostatic adenocarcinoma and cell proliferation in prostatic carcinoma cell lines has been shown to be modulated by peptides or biogenic amines, their analogs or antagonists [12,13].

Approximately 50% of all prostatic cancers contain neuroendocrine cells. The tumors with neuroendocrine features exhibit a spectrum of differentiation, ranging from differentiated adenocarcinoma to poorly differentiated carcinoma with neuroendocrine properties. These findings cannot be attributed to small cell prostatic carcinoma or carcinoid-like tumors, which represent only 1–2% of all prostatic malignancies [14]. It has been suggested that patients with tumors presenting signs of neuroendocrine tissue differentiation or with elevated plasma chromogranin A or NSE concentrations have a poorer prognosis than those not presenting this type of differentiation [15,16]. By contrast, expression of eutopic and/or ectopic peptide hormones in prostatic carcinoma was not associated with the "highest malignancy potential," as evidenced by determination of tumor DNA ploidy [17,18].

Some investigators, including ourselves, have previously reported that serum levels of neuroendocrine markers, particularly chromogranin A, could reflect the neuroendocrine activity of prostatic carcinoma and could be used during follow-up evaluation of advanced prostatic carcinoma. The presence of neuroendocrine differentiation in prostatic carcinoma has also suggested that new treatment strategies, such as antipeptidergic therapy, could be evaluated and developed. We have previously shown that during hormonal escape of prostatic carcinomas, which express high levels of chromogranin A, also express somatostatin receptors, as determined by Octreoscan® (personal communication). Neuroendocrine differentiation may therefore respond particularly well to somatostatin therapy or new antagonist peptide analogues [19].

PROSTATE NEUROENDOCRINE-LIKE PHENOTYPE

In 1985, di Sant'Agnese [20,21] defined the concept of prostatic neuroendocrine cells (also known as endocrine-paracrine cells, or APUD cells) as intraepithelial regulatory cells with hybrid neural endocrine and epithelial characteristics. These cells contain serotonin and a variety of peptides and are distributed throughout the prostate and urethra. At the same time, Per-Anders Abrahamsson summarized the histologic and cytologic patterns of NE cells in the prostate gland as following: "Ideally, a NE cell is defined as a cell of neuronal or epithelial type that fulfills all or most of the following criteria: it contains secretion granules; its secretion is essentially directed towards the blood; the secretion granules store peptide hormones and/or biogenic amines, as shown by IHC techniques; it is often argyrophil or even argentaffin, and is immunoreactive to antisera against neuron-specific enolase (NSE) or chromogranin A or other so-called NE markers."

Neuroendocrine differentiation in prostatic carcinoma is expressed in several forms, such as neuroendocrine small cell carcinoma, carcinoid-like tumors, and the focal neuroendocrine differentiation commonly observed in conventional prostatic adenocarcinoma. There is evidence that neuroendocrine differentiation in conventional prostatic adenocarcinoma could be associated with a poor prognosis and resistance to antiandrogen therapy. Small cell carcinoma pursues an aggressive course and id independent of androgen depletion.

PHENOTYPES AND FUNCTIONS OF PROSTATIC NEUROENDOCRINE-LIKE CELLS

Prostatic neuroendocrine cells contain a large variety of neurosecretory granules, suggesting multiple different cell types. Some are present in most neuroendocrine cells, such as serotonin, the chromogranin

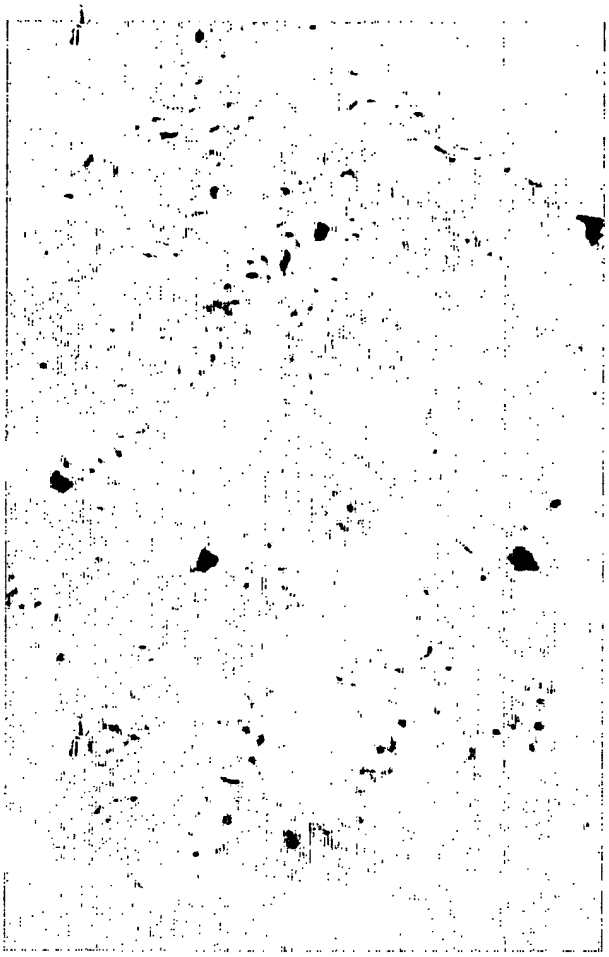

Fig. 1. Chromogranin A immunostaining in normal prostate. Neuroendocrine cells, chromogranin A-positive cells, are dispersed in the basal layer of acini and ducts.

family, including chromogranin A, chromogranin B, and secretogranin II (chromogranin C), and thyroid-stimulating hormone-like peptide, whereas others are present in smaller subpopulations of neuroendocrine cells, such as the calcitonin gene family, including calcitonin, katacalcin, and calcitonin gene-related peptide, parathyroid hormone-related protein (PTHrP), α-human chorionic gonadotropin-like peptide, or neurotensin. Finally, some peptides are inconsistently present in some neuroendocrine cells, such as bombesin, gaitrin-releasing peptide, or somatostatin.

Neuroendocrine cells are present in both normal and hyperplastic prostate. NE cells are located in the basal layer of the acini and in the ducts (Fig. 1). NE cells are most numerous in the periurethral zone of the prostate [20,21]. Some findings suggest that neuroendocrine cells of the peripheral prostate and utricle may be directly or indirectly androgen-dependent, whereas those in the periurethral region and prostatic ducts are not. A.T.K. Cockett [22] showed that small

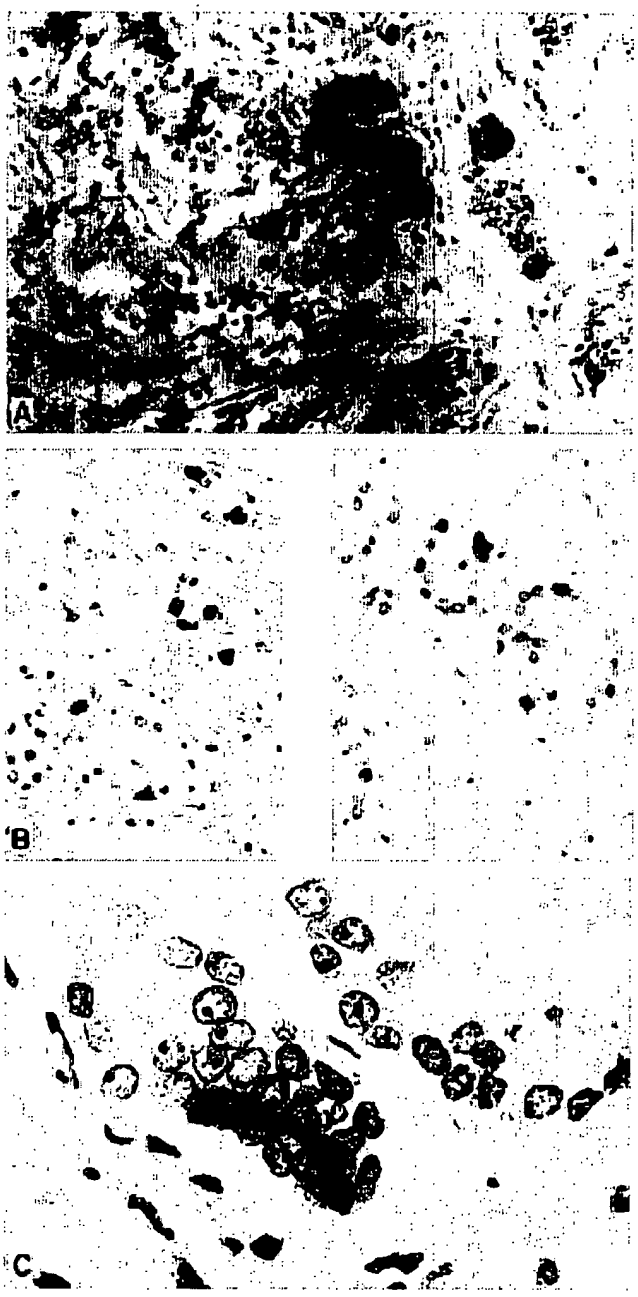

Fig. 2. Immunostaining of neuroendocrine-like cells in prostate carcinoma. **A:** Chromogranin A immunostaining in hormone-refractory prostate cancer. **B:** Chromogranin A and neuron-specific enolase immunostaining in organ-confined prostate cancer. **C:** Chromogranin A-positive cell exhibiting a morphological patterns of motility cell in prostate cancer.

proliferating nodules of benign prostatic hyperplasia contain abundant serotonin-positive endocrine-paracrine cells [3].

At the cellular level, staining of neuroendocrine cells by antibodies differs according to the marker. For example, NSE is localized in the cytosol, whereas

chromogranin A is localized in secretory granules of cells and synaptophysin is an integral membrane protein of presynaptic vesicles.

Coexpression of neuroendocrine markers and prostate markers, such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP), has been demonstrated and colocalized in neuroendocrine-like prostatic tumor cells. No case of concomitant expression of prostate membrane antigen (PSMA) and neuroendocrine markers has yet been reported. One study showed that basal cell cytokeratins were expressed in benign prostatic neuroendocrine cells. The coexpression of prostate epithelial specific markers and neuroendocrine markers would support the hypothesis of a common stem cell origin for basal, secretory and neuroendocrine cell types in the prostate. Bonkhoff et al. [23] demonstrated that the neuroendocrine phenotype in prostate carcinoma, as assessed by chromogranin A Immunoreactivity, represents an androgen-independent pS2-positive (estrogen-inducible protein), but postmitotic cell subpopulation, as assessed by proliferation associated MIB-1 antigen immunoreactivity [24]. Other evidence includes the demonstration that tumor cells in the vicinity of neuroendocrine tumor cells have an androgen independent behavior. Several immunocytochemical studies recently showed that the androgen receptor is not expressed in either normal or neoplastic neuroendocrine cells, suggesting that they may function independently of androgen regulation. This may explain why neuroendocrine tumor cells play a more prominent regulatory role in androgen-deprived tumors. Using a prostate cancer xenograft model, Noordzij et al. [25] showed that short-term androgen withdrawal resulted in a rapidly increased number of androgen-independent neuroendocrine-like cells. Moreover, the same distribution of neuroendocrine marker immunoreactivity and Bcl2 protein, which is an antiapoptotic factor, has been shown in lung cancers and possibly also in neural crest derived tumors [26]. In prostatic carcinoma, Bcl2 tends to be associated with foci of neuroendocrine differentiation [27].

Several growth factors involved in prostatic biology or pathobiology, such as IGF-I, IGF-II, and transforming growth factor (TGF-β), have been detected in carcinoid tumors [28], leading to investigation of coexpression of neuroendocrine markers and growth or angiogenic regulatory peptides in transformed prostatic cells lines and prostatic carcinoma. Neuroendocrine cells in normal and neoplastic prostate are devoid of androgen receptors but express epidermal growth factor receptor (EGFR) and c-erbB-2. It has been shown that epidermal growth factor (EGF) regulates PTHrP secretion and that PTHrP regulates EGFR expression. Expression of angiogenic factors platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) has been demonstrated in neuroendocrine tumors of the digestive system [29,30] and in small cell lung carcinomas. Harper et al. [31] showed intense granular cytoplasmic staining for VEGF in a cluster of neuroendocrine-like cells in prostate carcinoma and a similar distribution of VEGF and CgA-positive cells, suggesting coexpression in some cells. In the same study, a subpopulation of neuroendocrine-like cells was intensely stained with TGFα antibody and a correlation was demonstrated between the number of these cells and the total population of neuroendocrine cells as identified by chromogranin A localization. Recently, TGF-α has been reported to be expressed in various neuroendocrine tumors, including carcinoid tumors of the midgut, medullary thyroid carcinomas and pheochromocytomas [32].

Several prostatic cell lines express neuroendocrine markers. We have shown that androgen-sensitive and androgen-insensitive epithelial prostatic cell lines, including immortalized prostatic cells PNT1, and transformed cell lines such as PC3, LNCaP, and DU145, secrete various neuroendocrine substances, especially NSE, calcitonin, and substance P. Low expression of PTHrP, bombesin, neurotensin, or somatostatin was identified in these cell lines [33], but a high serotonin level (5,560 pM/mg) was found in three dimensional cultures of LNCaP cell line (unpublished data). The growth of all three prostatic cell lines, PC3, DU145, and LNCaP, has been shown to be inhibited by selective serotonin receptor antagonists such as pindobind [34]. Interestingly, it has been demonstrated that biogenic amines, particularly dopamine, can mimic the effect of sex steroid hormones by causing translocation of the receptor from cytoplasm to nucleus with a physiologic action. Other investigators have shown that PC3, LNCaP, and DU145 cell lines coexpressed chromogranin A, NSE, and serotonin, with urokinase and heparinase, which are extracellular matrix degradation enzymes involved in metastatic ability. No report have linked neuroendocrine-like phenotype and cell motility. Neuroendocrine cells are known for their ability to migrate during ontogenesis. Figure 2C depicts a chromogranin A-positive cell that suggested a morphology of motility cell. Some peptides may inhibit growth (e.g., somatostatin), while others may stimulate growth (e.g., PTHrP and bombesin). It is critical to look for receptors for these substances on both neuroendocrine and non-neuroendocrine cells, as they constitute a key component of autocrine/paracrine loops. Furthermore, Bang et al. [35] showed that a terminal neuroendocrine differentiation could be induced in the two human prostate carcinoma cell lines (PC3 and LNCaP) by increasing intracellular cyclic AMP. Treatment of theses cells by dibutyry AMP

markedly elevated some neuroendocrine markers (NSE and $pp60^{c\text{-}src}$) and induced growth arrest and loss of clonogenicity.

NEUROENDOCRINE DIFFERENTIATION IN CLINICAL OUTCOME OF PROSTATE CANCERS

di Sant'Agnese and Cockett [3] classified neuroendocrine differentiation in prostatic malignancies into three forms on the basis of histologic features, including the rare small cell anaplastic neuroendocrine carcinoma and carcinoid-like tumors, and the frequent neuroendocrine differentiation associated with common prostatic adenocarcinoma. If we consider clinical and biological aspects of neuroendocrine differentiation of prostatic carcinoma and the fact that neuroendocrine-like cells are usual during progression of the disease, three neuroendocrine phenotypes for clinical prostatic carcinoma can be distinguished: (1) the rare endocrine paraneoplastic syndromes associated with prostatic carcinoma; (2) prostatic carcinoma without clinical paraneoplastic signs, but with humoral expression of neuroendocrine tumor differentiation, as assessed by plasma neuroendocrine markers concentration; (3) and prostatic carcinoma without clinical or humoral expression of neuroendocrine markers, but with histopathologic features of neuroendocrine differentiation.

Paraneoplastic syndromes occur in some patients with prostate cancer. These syndromes must be recognized, as they may constitute the first sign of malignancy. The commonest endocrine syndrome associated with prostatic carcinoma is Cushing's syndrome with ectopic secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing factor (CRF). The first case was reported by Wise et al. [36] in 1959. In a study by Ghali and Garcia [37], most prostatic carcinomas associated with Cushing's syndrome were poorly differentiated adenocarcinomas. Other histopathological features have been reported in association with inappropriate ACTH expression, such as small cell carcinoma [38] or carcinoid tumors [39]. Schwartz-Bartter syndrome (SBS), resulting from inappropriate antidiuretic hormone (ADH), is the commonest paraneoplastic syndrome associated with small cell lung carcinoma. SBS associated with prostatic adenocarcinoma was reported for the first time in 1969, by Selwood et al. [40]. Other investigators have reported inappropriate ADH syndrome and have characterized the prostatic tumor as adenocarcinoma or [41] undifferentiated carcinoma [42]. The most frequent serum calcium disturbance in prostatic carcinoma is hypocalcemia, due to metastatic osteosclerosis or bone demineralization after a long period of androgen depletion. Hypercalcemia during prostatic carcinoma is a rare occurrence and was reported by Shulkes et al. [43] to be linked with PTH, calcitonin and gastrin during the course of a poorly differentiated prostatic adenocarcinoma.

Determination of neuroendocrine marker expression in the primary tumor remains controversial, since, as indicated in this study, staining is always heterogeneous and often localized or focal (Fig. 2A,B). The detection of neuroendocrine markers in the blood of patients with prostatic carcinoma certainly constitutes a more global indicator and more objective quantification of significant neuroendocrine differentiation of tumors, as it corresponds to the entire primary tumor and its associated metastases. Elevated plasma neuroendocrine cell products (chromogranin A and NSE) have been described in some patients [44,45]. They may possibly originate from a prostatic carcinoid subpopulation dispersed within common epithelial structures. Positive plasma values of ectopic (NSE, chromogranin A, substance P, and bombesin) and eutopic markers (PSA and PAP) therefore seem to at least reflect different clones and indicate the presence of a neuroendocrine prostatic cancer cell subpopulation. Angelsen et al. [46] demonstrated a correlation between the number of chromogranin A-positive NE cells and serum chromogranin A levels in patients with prostatic carcinoma. Serum chromogranin A level must be interpreted cautiously in patients with impaired renal function or in those receiving treatment for peptic ulcer with drugs such as omeprazole, as these particular situations can induce elevated serum chromogranin A. Kadmon et al. [44] reported that plasma chromogranin A levels were elevated in 48% patients with metastatic stage of prostate cancer. Similarly, Logothetis and Hoosi [47] found that 47% of patients treated for androgen-independent growth of classical prostatic adenocarcinoma had significantly elevated plasma bombesin levels, although raised bombesin levels were rarely detected in our experience (only 7% patients with androgen independent disease) [16]. In Kadmon's study, the frequency of high chromogranin A levels (17% of patients with advanced prostatic disease in our study) and the fact that the conventional PSA and PAP markers were normal in an unusually high percentage (33%) of patients with metastatic prostate cancers, suggested that this group of patients was not representative of usual progressive tumor status. Our previous study on 135 prostate cancer patients, in 1996, showed that 0% of patients with advanced prostatic cancer (including metastatic diseases) and 14% of patients with hormone-resistant cancer had a normal plasma PSA level, which is more representative of metastatic stages and of a hormonal escape profile. The fact that prostatic carcinomas ex-

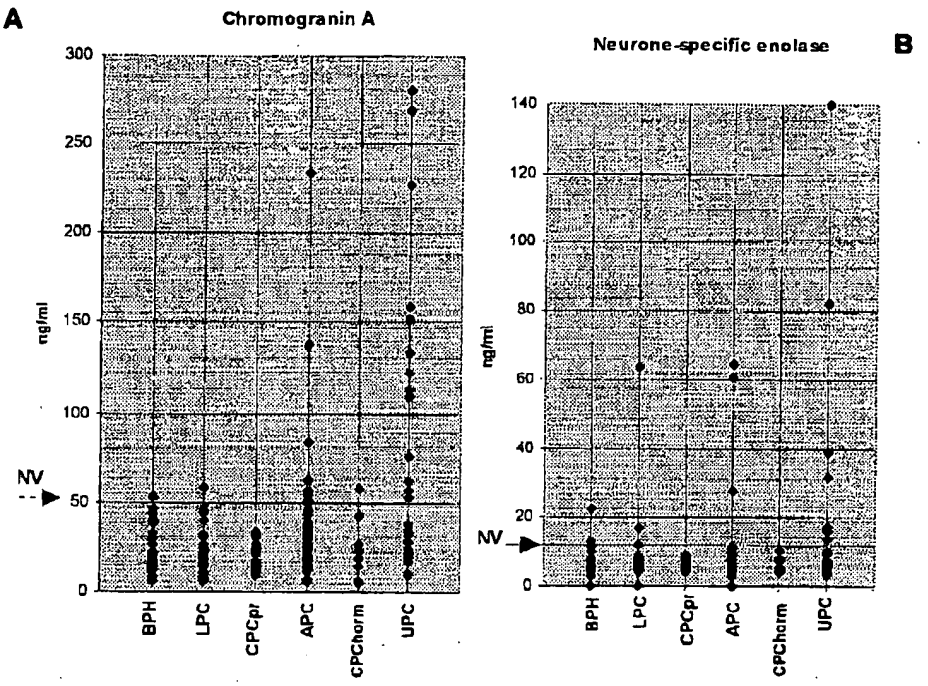

Fig. 3. Diagrams of chromogranin A **(A)** and neuron-specific enolase **(B)** serum level distribution in patients with benign prostate hyperplasia (BPH) and prostate cancer (PC). LPC, localized PC before treatment; CPCpr, PC controlled by radical prostatectomy; APC, advanced prostate cancer before treatment; CPChorm, PC controlled by androgen depletion; UCPC, uncontrolled PC by hormone therapy, hormonal escape. Normal value (NV) chromogranin A NV, 51 ng/ml; NSE NV, 10 ng/ml.

pressed neuropeptide markers (CgA, 17%; NSE, 15%) before any endocrine therapy shows that neuroendocrine products may be involved in PC progression independently of androgen withdrawal (Fig. 3A,B). Deftos et al. [48], in 1996, confirmed and completed previous studies with serum chromogranin A measurements in 82 patients with various stages of prostate cancer. These data [48], and a more recent report by Kimura et al. [49], demonstrated that chromogranin A could be useful, especially in advanced disease. The incidence of elevated NSE levels in patients with prostatic tumors was lower than that of elevated chromogranin A levels. Tarle and Rados [45] found that elevated plasma NSE levels were more frequent in untreated subjects with localized tumors (28.6%) than in untreated subjects with disseminated disease (10.7%). However, at least according to Cohen et al. [15], elevated NSE values were frequently present in nonresponders to hormone therapy. NSE levels were inversely correlated with stage in untreated PC patients, which contradicts other evidence suggesting that neuroendocrine differentiation is directly correlated with grade [14]. We found that elevated NSE levels were more frequent during hormonal escape (30%), but they did not have any prognostic value compared to chromogranin A expression (55%) and showed a poor concordance with immunohistochemical data [14,15].

Serum levels of chromogranin A, pancreastatin, a breakdown product of chromogranin A, chromogranin B (CBG) [46], and chromogranin C [50] were recently evaluated and compared as serum markers in the follow-up evaluation of patients with prostate cancer. Chromogranin A appears to be the best marker of neuroendocrine prostate tumor activity. However, in some poorly differentiated prostatic tumors, chromogranin B is the major component and could be expressed in poorly differentiated carcinomas that almost completely lack chromogranin A and chromogranin C, while serum chromogranin B levels did not provide any prognostic information.

Under the broad heading of neuroendocrine differentiation, histopathological features distinguish the particular and rare form of small cell carcinoma, carcinoid tumor, and the commonest neuroendocrine patterns associated with adenocarcinoma. Small cell carcinomas of the prostate constantly have a poorly prognosis with a reported median survival of only 5 months [51]. In 1991, using an immunohistochemical technique, Cohen et al. [15] suggested that neuroendocrine differentiation was a new independent prognostics factor for prostatic carcinoma. Berner et al. [52],

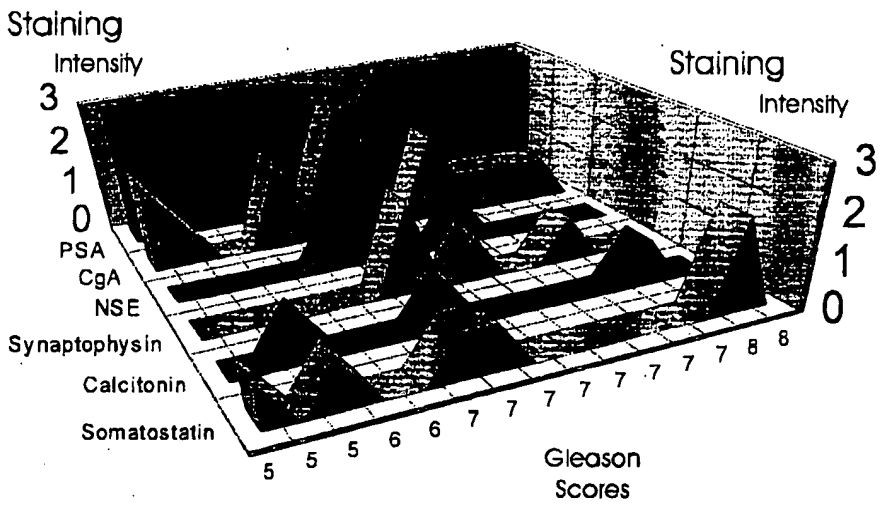

Fig. 4. Immunoreactivity of chromogranin A, neuron-specific enolase (NSE), Calcitonin, synaptophysin, and somatostatin, as well as prostate-specific antigen (PSA) in 15 radical prostatectomy specimens underwent for localized prostate cancers, each tumor has been analyzed for the Gleason score and the intensity of the staining has been quantified (from 0 to 3).

in 1993, showed that 32% of patients with initial neuroendocrine differentiation, as assessed by NSE immunoreactivity of prostate tumors, subsequently became resistant to hormone therapy; in 1994, the same investigators conducted a multivariate analysis of the prognosis significance of each of the above-mentioned factors (grade, PSA, PAP, NSE, c-erB-2, p53 protein, vimentin, and cytokeratins) in tissue sections from 131 cases of metastatic and localized prostate cancer. On the basis of survival analysis, these workers concluded on a trend toward decreased survival with decreasing PSA staining and extensive NSE reactivity. In a previous study, we analyzed biomarkers for neuroendocrine phenotype (chromogranin A, NSE, calcitonin, synaptophysin, and somatostatin) and PSA in order to compare the tumor heterogeneity for immunoreactivity of different type of biomarkers. The study was performed in 15 consecutive radical prostatectomy specimens that underwent localized prostate cancers; each tumor has been analyzed at five different levels and the intensity of the staining has been quantified (from 0 to 3) by three pathologists. The results summarized in Figure 4 show that chromogranin A was the neuroendocrine marker that was expressed the most frequently and that was the most easily to quantify [53]. Weinstein et al. [54], in 1995, suggested that the number of chromogranin A-reactive malignant cells could be a valuable and independent prognostic factor in a series of 104 patients who had undergone radical prostatectomy for organ-confined disease. On the other hand, Aprikian et al. [55] claimed that determination of neuroendocrine differentiation in prostatic cancer lymph node metastases did not have any significant prognostic value in stage D1 prostate cancer. Similarly, in a series of 38 stage II (AJCC) prostatic carcinomas treated by radical prostatectomy, Cohen et al. [15] demonstrated that neuroendocrine differentiation, as demonstrated by NSE and chromogranin A immunostaining, was not helpful in predicting tumor progression. More recently, Noordzij et al. [25] studied chromogranin A expression on 103 prostatectomy specimens and correlated the immunostaining quantification with the pathologic stage, Gleason score, and patient outcome with a mean follow-up of 86 months. The authors were unable to find any correlation between chromogranin A immunostaining score and pathologic stage or Gleason grade and did not establish any prognostic value.

CONCLUSIONS

Several investigators have reported that histopathologic determination of neuroendocrine differentiation in prostate carcinomas may have prognostic implications, while others have not confirmed these results. The fact that focal, patchy, and heterogeneous clusters of neuroendocrine-like cells are frequently identified in organ-confined prostatic carcinoma probably accounts for the various evaluations of the predictive value of neuroendocrine histological patterns for the clinical outcome at this stage of the disease. Furthermore, neuroendocrine differentiation is mostly focal, and small tissue specimens such as core biopsies may be inadequate to demonstrate such features. The amount of neuroendocrine cells required to produce a detectable elevation in plasma chromogranin A has not yet been determined, but it is correlated with the number of chromogranin A-positive NE cells. Despite the obvious current limitations of the application of neuropeptides as a serological test, this overview attempts to define more accurately the possible roles of specific neuropeptides as prostatic cancer markers in diagnostic and monitoring protocols. The plasma chromogranin A level, as compared with NSE, CBG, pancreastatin, or secretogranin levels, appears to be

the most useful neuroendocrine marker for determining neuroendocrine differentiation of advanced prostatic adenocarcinoma. The presence of elevated plasma levels of chromogranin A or other peptide profiles seems to be predictive of, or associated with, the development of resistance to hormonal suppression therapy, which is known to be associated with a particularly poor prognosis. Growth and production of autocrine-paracrine factors by neuroendocrine cells or neuronal differentiation of epithelial tumor cells are probably influenced by hormones and are involved in the progression of prostatic carcinoma. It has been postulated that long-term androgen ablative therapy produces an outgrowth of neuroendocrine cells in prostatic tumors. These findings suggest that determination of autocrine-paracrine neuropeptide production in prostatic carcinoma must be included in the development of new antipeptidergic therapy for prostatic carcinoma, including peptide analogs or Biamine antagonists. They could be useful to select patients during late progression of PC for treatment by drugs known to be active against neuroendocrine tumors.

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